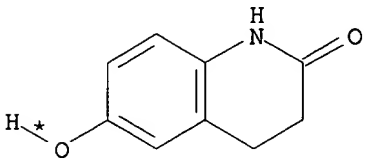
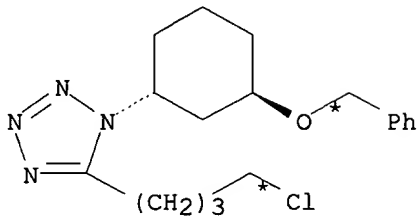
RX(39) RCT AY 98454-55-8
RGT BD 1333-74-0 H2
PRO BI **98360-33-9**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

RX(75) OF 147 COMPOSED OF RX(34), RX(40)
RX(75) AU + **AR** ===> **BJ**

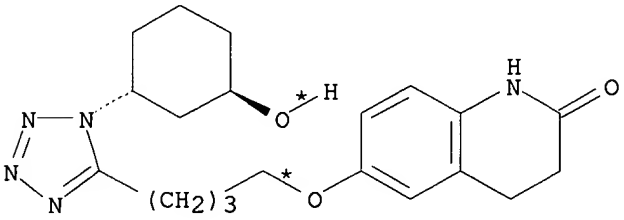


AU



AR

2 STEPS

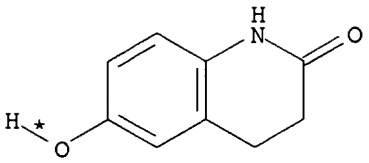


BJ

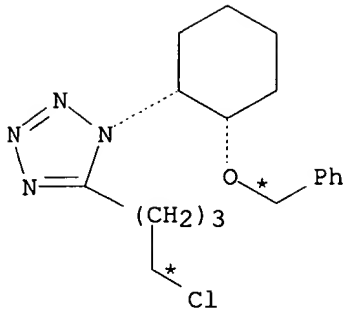
RX(34) RCT AU 54197-66-9, AR **98454-52-5**
RGT U 1310-58-3 KOH
PRO AZ 87153-00-2
SOL 67-63-0 Me2CHOH

RX(40) RCT AZ 87153-00-2
RGT BD 1333-74-0 H2
PRO BJ **98360-32-8**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

RX(76) OF 147 COMPOSED OF RX(35), RX(41)
RX(76) AU + **AS** ===> **BK**

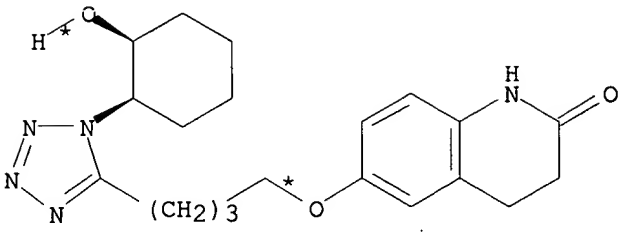


AU



AS

2 STEPS

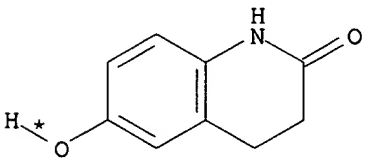


BK

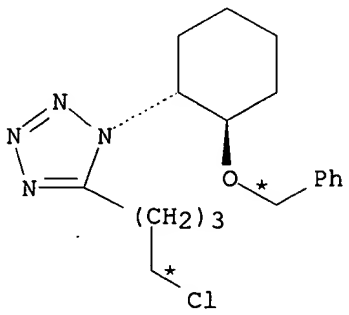
RX(35) RCT AU 54197-66-9, AS **98454-53-6**
RGT U 1310-58-3 KOH
PRO BA 87152-98-5
SOL 67-63-0 Me2CHOH

RX(41) RCT BA 87152-98-5
RGT BD 1333-74-0 H2
PRO BK **87153-05-7**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

RX(77) OF 147 COMPOSED OF RX(36), RX(42)
RX(77) AU + **AT** ===> **BL**

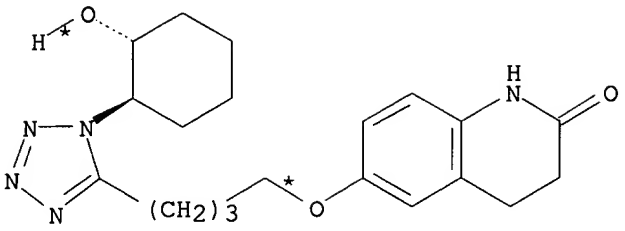


AU



AT

2 STEPS

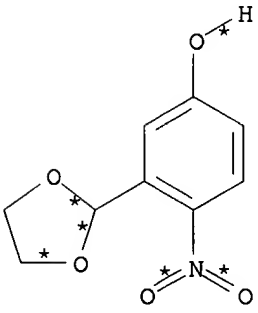


BL

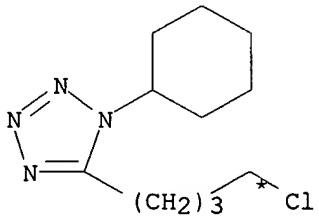
RX(36) RCT AU 54197-66-9, AT **87153-14-8**
RGT U 1310-58-3 KOH
PRO BB 87153-12-6
SOL 67-63-0 Me2CHOH

RX(42) RCT BB 87153-12-6
RGT BD 1333-74-0 H2
PRO BL **87153-03-5**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

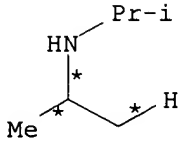
RX(128) OF 147 COMPOSED OF RX(44), RX(45), RX(46), RX(47)
RX(128) BO + **BR** + BV + BW ===> **CA**



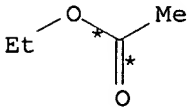
BO



BR

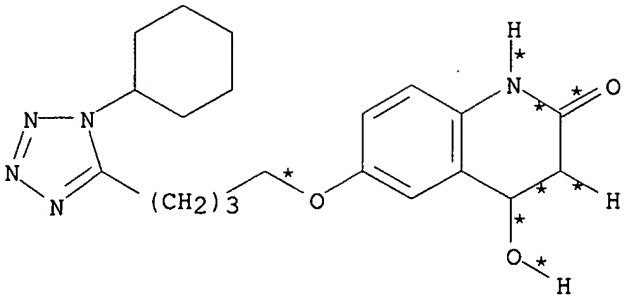


BV



BW

4
STEPS



CA

RX(44) RCT BO 98454-56-9, BR **73963-42-5**
RGT AE 584-08-7 K2CO3
PRO BS 98454-57-0
SOL 68-12-2 DMF

RX(45) RCT BS 98454-57-0
RGT BU 7647-01-0 HCl
PRO BT 98454-58-1
SOL 7732-18-5 Water

RX(46) RCT BV 108-18-9

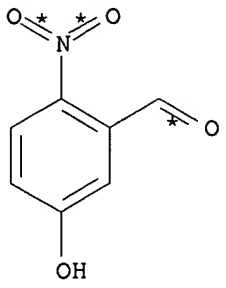
STAGE(1)
RGT BY 109-72-8 BuLi
SOL 109-99-9 THF, 7440-37-1 Ar

STAGE(2)
RCT BW 141-78-6

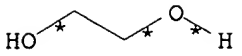
STAGE(3)
RCT BT 98454-58-1
SOL 108-88-3 PhMe
PRO BX 93662-05-6

RX(47) RCT BX 93662-05-6
RGT CB 7664-41-7 NH3, CC 7720-78-7 FeSO4
PRO CA **93632-84-9**
SOL 64-17-5 EtOH, 7732-18-5 Water

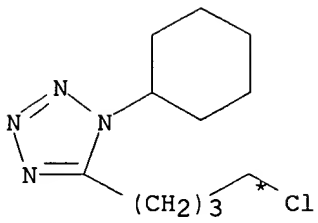
RX(147) OF 147 COMPOSED OF RX(43), RX(44), RX(45), RX(46), RX(47)
RX(147) BM + BN + **BR** + BV + BW ===> **CA**



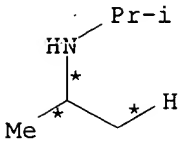
BM



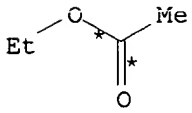
BN



BR

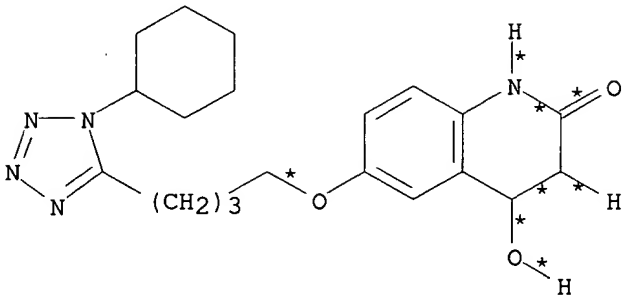


BV



BW

5 STEPS



CA

RX(43) RCT BM 42454-06-8, BN 107-21-1
RGT BP 122-51-0 CH(OEt)3, BQ 104-15-4 TsOH
PRO BO 98454-56-9
SOL 107-21-1 (CH2OH)2

RX(44) RCT BO 98454-56-9, BR **73963-42-5**
RGT AE 584-08-7 K2CO3
PRO BS 98454-57-0
SOL 68-12-2 DMF

RX(45) RCT BS 98454-57-0
RGT BU 7647-01-0 HCl
PRO BT 98454-58-1
SOL 7732-18-5 Water

RX(46) RCT BV 108-18-9

STAGE(1)
RGT BY 109-72-8 BuLi

SOL 109-99-9 THF, 7440-37-1 Ar

STAGE(2)
RCT BW 141-78-6

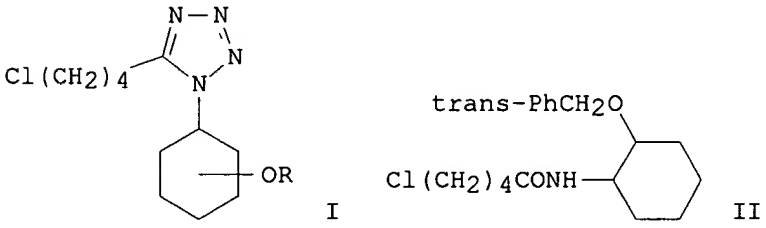
STAGE(3)
RCT BT 98454-58-1
SOL 108-88-3 PhMe
PRO BX 93662-05-6

RX(47) RCT BX 93662-05-6
RGT CB 7664-41-7 NH3, CC 7720-78-7 FeSO4
PRO CA **93632-84-9**
SOL 64-17-5 EtOH, 7732-18-5 Water

L3 ANSWER 4 OF 6 CASREACT COPYRIGHT 2002 ACS ✓
ACCESSION NUMBER: 99:194975 CASREACT
TITLE: Tetrazole derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58062168	A2	19830413	JP 1981-161386	19811009
JP 01060024	B4	19891220		

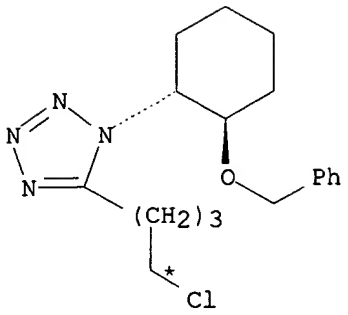
GI



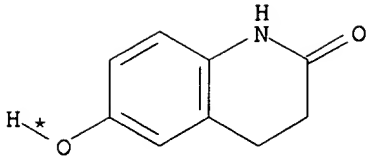
I II

AB Tetrazole derivs. I (R = 2-trans-PhCH2, 2-cis-PhCH2, 4-cis-PhCH2, 4-trans-PhCH2, 3-trans-PhCH2, 2-trans-Me) were prepd. Thus, addn. of 6.7 g PCl5 to 9.5 g II in C6H6 with ice cooling, stirring the mixt. 1 h at room temp., addn. of 100 mL 0.345 N HN3/C6H6 with ice cooling, and stirring the whole overnight at room temp. gave 4.8 g I (R = 2-trans-PhCH2).

RX(3) OF 4 ...**B** + D ===> **E**

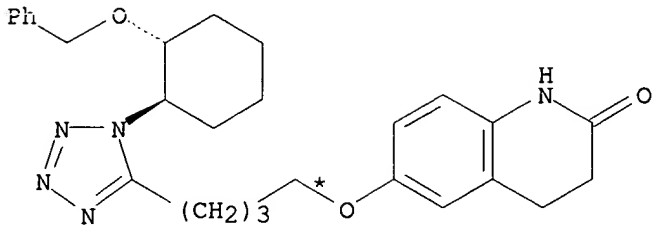


B



D

(3) →



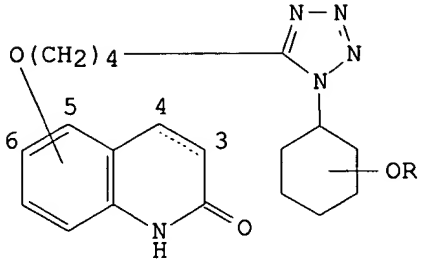
E

RX(3) RCT B **87153-14-8**, D 54197-66-9
PRO E **87153-12-6**

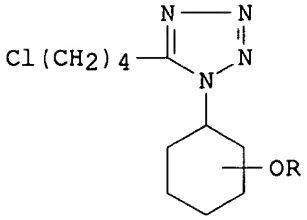
L3 ANSWER 5 OF 6 CASREACT COPYRIGHT 2002 ACS
ACCESSION NUMBER: 99:175770 CASREACT
TITLE: Carbostyrils
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58059980	A2	19830409	JP 1981-158927	19811005
JP 64000397	B4	19890106		

GI



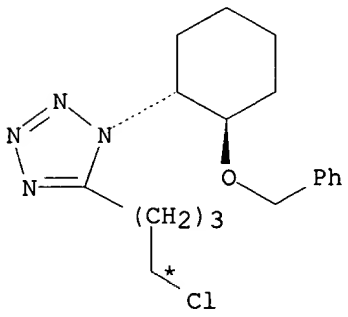
I



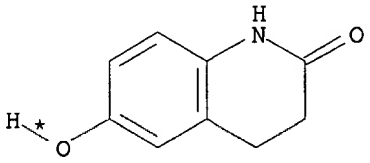
II

AB Sixteen I [5- or 6-substituted, R = CH2Ph, H, Ac, Me, (substituted) benzoyl] were prepd., e.g., by reaction of the appropriate hydroxycarbostyrils with II. Thus, refluxing 6-hydroxy-3,4-dihydrocarbostyril with II (OR = 2-trans-OCH2Ph) [obtained by cyclocondensation of trans-1-(benzyloxy)-2-(5-chlorohexanamido)cyclohexane with HN3] in Me2CHOH contg. KOH for 5 h gave I (6-substituted, OR = 2-trans-OCH2Ph, 3,4-dihydro). Some I at 10-4 M concn. inhibited blood platelet aggregation induced by collagen and ADP by 80.5-95.2 and 55.3-95.2%, resp.

RX(2) OF 3 ...**B** + C ===> **D**

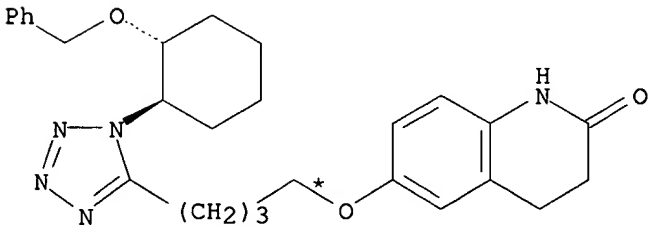


B



C

(2) →



D

RX(2) RCT B **87153-14-8**, C 54197-66-9
PRO D **87153-12-6**

L3 ANSWER 6 OF 6 CASREACT COPYRIGHT 2002 ACS ✓

ACCESSION NUMBER: 99:98806 CASREACT

TITLE: Studies on 2-oxoquinoline derivatives as blood platelet aggregation inhibitors. II. 6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline and related compounds

AUTHOR(S): Nishi, Takao; Tabusa, Fujio; Tanaka, Tatsuyoshi; Shimizu, Takefumi; Kanbe, Toshimi; Kimura, Yukio; Nakagawa, Kazuyuki

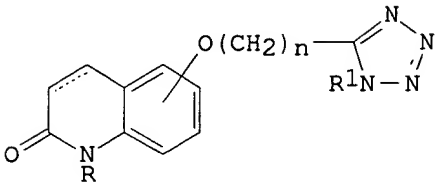
CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan

SOURCE: Chem. Pharm. Bull. (1983), 31(4), 1151-7
CODEN: CPBTAL; ISSN: 0009-2363

DOCUMENT TYPE: Journal

LANGUAGE: English

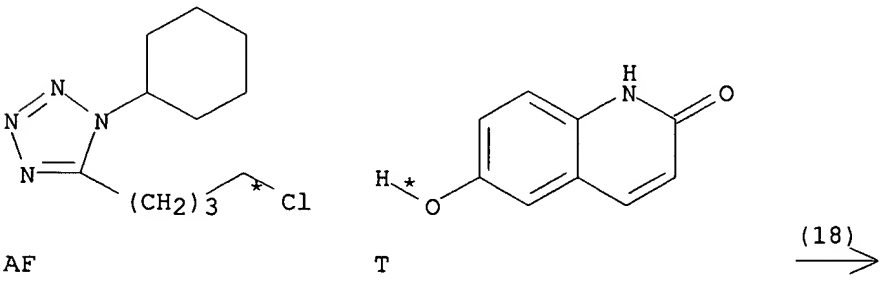
GI



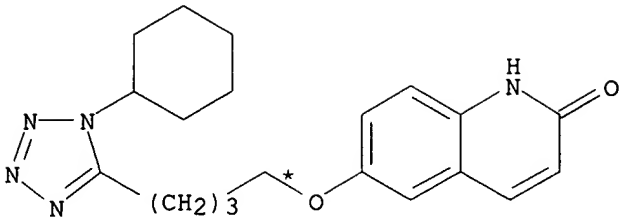
I

AB A series of .omega.-(1-substituted-5-tetrazolylalkoxy)-2-oxo-tetrahydro- or dihydro-quinolines I (R = H, Me, Et, COMe, etc; R1 = H, cyclohexyl, Et, cyclooctyl, alkylpyridine, etc.) were synthesized and tested for inhibitory activity towards collagen- and ADP-induced aggregation of rabbit blood platelets in vitro. These compds. were prepd. by the reaction of 1-substituted-5-(.omega.-chloroalkyl)-tetrazoles and hydroxy-2-oxoquinolines in the presence of a base. Among them, 6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline (I; R = H, R1 = cyclohexyl) [73963-46-9] was found to have the most potent inhibitory activity. The structure-activity relationships are discussed.

RX(18) OF 89 ...**AF** + T ===> **AG**



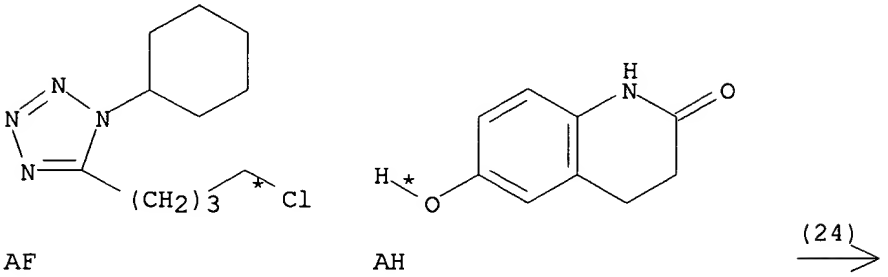
AF T (18)



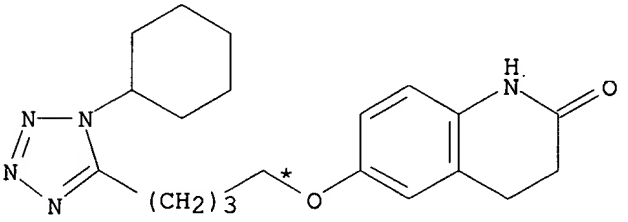
AG
YIELD 37%

RX(18) RCT AF **73963-42-5**, T 19315-93-6
PRO AG **73963-62-9**

RX(24) OF 89 ...**AF** + AH ===> **AO**



AF AH (24)



AO
YIELD 74%

RX(24) RCT AF **73963-42-5**, AH 54197-66-9
PRO AO **73963-72-1**

=> file caplus
FILE 'CAPLUS' ENTERED AT 11:27:04 ON 16 SEP 2002

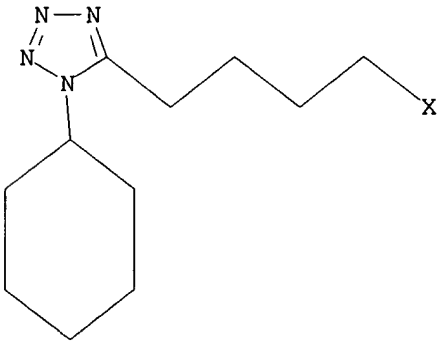
FILE COVERS 1907 - 16 Sep 2002 VOL 137 ISS 12
FILE LAST UPDATED: 15 Sep 2002 (20020915/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d que
L4 STR
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.
L5 STR



Structure attributes must be viewed using STN Express query preparation.
L7 28 SEA FILE=REGISTRY SSS FUL L4
L8 15 SEA FILE=REGISTRY SSS FUL L5
L9 7 SEA FILE=CAPLUS L7 AND L8

=> d l9 1-7 ibib abs hit

L9 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:142678 CAPLUS
DOCUMENT NUMBER: 136:183828
TITLE: Preparation of cilostazol
INVENTOR(S): Mendelovichi, Marioara; Finkelstein, Nina; Pilarksi, Gideon
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014283	A1	20020221	WO 2001-US25398	20010814

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001084887	A5	20020225	AU 2001-84887	20010814
US 2002099213	A1	20020725	US 2001-929683	20010814

PRIORITY APPLN. INFO.: US 2000-225362P P 20000814
US 2000-190588P P 20000320
WO 2001-US25398 W 20010814

OTHER SOURCE(S): CASREACT 136:183828

AB The present invention provides processes for prepg. cilostazol {6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone} and processes for purifying the same by recrystn. Thus, 6-hydroxy-3,4-dihydroquinolinone, KOH, K2CO3, 5-(4-chlorobutyl)-1-cyclohexyl-1H-tetrazole, and n-BuOH are heated at reflux for 5 h to give 84% cilostazol. Cilostazol inhibits cell platelet aggregation and is used to treat patients with intermittent claudication (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **73963-72-1P**, Cilostazol
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of cilostazol)

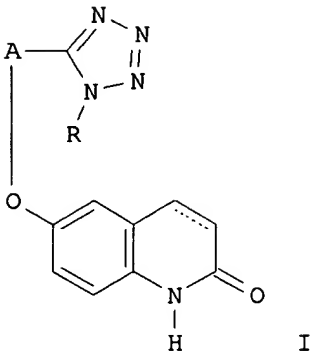
IT 54197-66-9 **73963-42-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of cilostazol)

L9 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:568372 CAPLUS
DOCUMENT NUMBER: 135:137510
TITLE: Process for the preparation of tetrazolylalkoxycarbostyril derivatives
INVENTOR(S): Aki, Shinji; Kurimura, Muneaki; Nishi, Takao; Nankawa, Junichi; Tominaga, Michiaki; Fukuyama, Norihiro; Yamamoto, Akihiro
PATENT ASSIGNEE(S): Ohtsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001213877	A2	20010807	JP 2000-339018	20001107

PRIORITY APPLN. INFO.: JP 1999-332559 A 19991124
OTHER SOURCE(S): CASREACT 135:137510; MARPAT 135:137510
GI



I

AB The title compds. I [A = alkylene; R = cycloalkyl; the dotted line indicates a single or double bond] are prepd., e.g. by reaction of 6-hydroxy-3,4-dihydrocarbostyril with a haloalkyltetrazole deriv. in the presence of a phase transfer catalyst (e.g., tetrabutylammonium chloride). I are useful as antithrombotics, inflammation inhibitors, antiulcer agents (no data), etc. 6-[4-(1-Cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril was prepd. in 95% yield by the title process.

IT **73963-72-1P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for prepn. of tetrazolylalkoxycarbostyril derivs.)

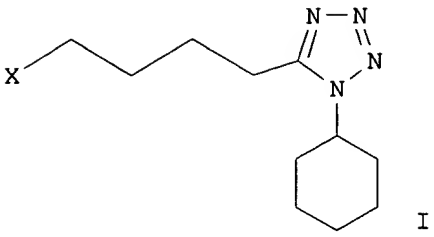
IT 19315-93-6, 6-Hydroxycarbostyril 54197-66-9, 6-Hydroxy-3,4-dihydrocarbostyril **73963-42-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for prepn. of tetrazolylalkoxycarbostyril derivs.)

L9 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:585431 CAPLUS
DOCUMENT NUMBER: 133:150564
TITLE: Preparation of 5-halobutyl-1-cyclohexyltetrazoles
INVENTOR(S): Lee, Byon Suku; Yoo, Ji Sun
PATENT ASSIGNEE(S): Kyung Dong Pharm Co., Ltd., S. Korea
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2000229953	A2	20000822	JP 1999-108015	19990415
KR 2000055711	A	20000915	KR 1999-4468	19990209

PRIORITY APPLN. INFO.: KR 1999-4468 A 19990209
OTHER SOURCE(S): CASREACT 133:150564; MARPAT 133:150564
GI



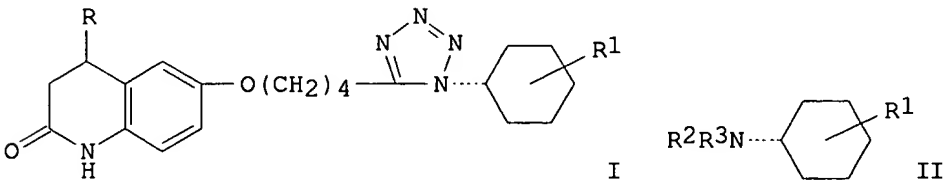
I

AB Title compds. I (X = Cl, Br, iodo), useful as intermediates for the thrombolytic cilostazol, are prepd. by reaction of N-cyclohexyl-5-hydroxypentanamide with sodium azide. Thus, reaction of .delta.-valerolactone with cyclohexylamine at 150.degree. for 2 h gave 97% N-cyclohexyl-5-hydroxypentanamide, chlorination of which with PCl5 in CH2Cl2 followed by refluxing with NaN3 gave 92% I (X = Cl).

IT **73963-42-5P** 84996-93-0P **287714-28-7P** **287714-29-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 5-halobutyl-1-cyclohexyltetrazole)

IT **73963-72-1P**, Cilostazol
RL: PNU (Preparation, unclassified); PREP (Preparation)
(prepn. of 5-halobutyl-1-cyclohexyltetrazole as intermediate for cilostazol)

L9 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:541893 CAPLUS
DOCUMENT NUMBER: 103:141893
TITLE: Studies on 2-oxoquinoline derivatives as blood platelet aggregation inhibitors. IV. Synthesis and biological activity of the metabolites of 6-[4-(1-cyclohexyl-1H-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (OPC-13013)
AUTHOR(S): Nishi, Takao; Tabusa, Fujio; Tanaka, Tatsuyoshi; Shimizu, Takefumi; Nakagawa, Kazuyuki
CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan
SOURCE: Chem. Pharm. Bull. (1985), 33(3), 1140-7
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 103:141893
GI



I

II

AB Metabolites of (I; R = R1 = H) were prepd. Thus, cyclohexanolamides II (R1 = 2.alpha.-, 2.beta.-, 3.alpha.-, 3.beta.-, 4.alpha.-, 4.beta.-OH, R2 = H, R3 = Ac) were benzylated to give 61-84% II (R1 = OCH2Ph), which were hydrolyzed to give 76-89% II (R1 = OCH2Ph, R2 = R3 = H). Acylation of the

amines with Cl(CH2)4COCl gave 80-98% II [R1 = OCH2Ph, R2 = H, R3 = CO(CH2)4Cl], which typically gave .apprx.95% II [R2R3 = N:NN:C(CH2)4Cl] upon treatment with PCl5-HN3. Coupling of these compds. with 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline, followed by hydrogenolysis, gave I (R = H, R1 = OH). I (R = OH, R1 = H) was also prepd. in 5 steps from 5,2-HO(O2N)C6H3CHO. I (R = H, R1 = 3.alpha.-, 4.alpha.-, 4.beta.-OH; R = OH, R1 = H) were identified as metabolites of OPC-13013, with I (R = H, R1 = 3.alpha.-4.alpha.-OH) showing almost equiv. platelet aggregation-inhibitory activities.

IT **89332-50-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(metabolites of, prepn. and platelet aggregation-inhibiting activity of)

IT **87152-97-4P 87152-98-5P 87153-00-2P 87153-12-6P 98454-54-7P 98454-55-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrogenolysis of)

IT **87153-03-5P 87153-04-6P 87153-05-7P 87153-06-8P 93632-84-9P 98360-32-8P 98360-33-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and inhibition of platelet aggregation by)

IT **87153-14-8P 98454-49-0P 98454-50-3P 98454-51-4P 98454-52-5P 98454-53-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and O-alkylation by, of hydroxytetrahydroquinolinone)

IT **73963-42-5**
RL: RCT (Reactant)
(O-alkylation by, of hydroxynitrobenzaldehyde acetal)

L9 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:575770 CAPLUS
DOCUMENT NUMBER: 99:175770
TITLE: Carbostyrils
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58059980	A2	19830409	JP 1981-158927	19811005
JP 64000397	B4	19890106		

OTHER SOURCE(S): CASREACT 99:175770
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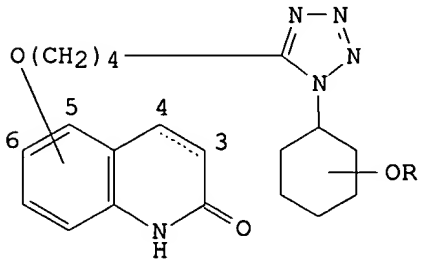

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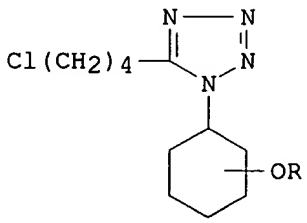


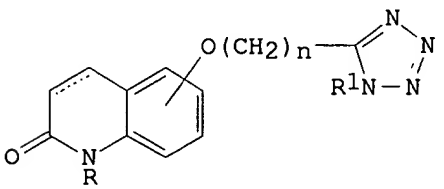
II

AB Sixteen I [5- or 6-substituted, R = CH2Ph, H, Ac, Me, (substituted) benzoyl] were prepd., e.g., by reaction of the appropriate hydroxycarbostyrils with II. Thus, refluxing 6-hydroxy-3,4-dihydrocarbostyril with II (OR = 2-trans-OCH2Ph) [obtained by cyclocondensation of trans-1-(benzyloxy)-2-(5-chlorohexanamido)cyclohexane with HN3] in Me2CHOH contg. KOH for 5 h gave I (6-substituted, OR = 2-trans-OCH2Ph, 3,4-dihydro). Some I at 10-4 M concn. inhibited blood platelet aggregation induced by collagen and ADP by 80.5-95.2 and 55.3-95.2%, resp.

IT **87153-14-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and etherification by, of hydroxycarbostyril deriv.)

IT **87152-97-4P 87152-98-5P 87152-99-6P**
87153-00-2P 87153-01-3P 87153-02-4P
87153-03-5P 87153-04-6P 87153-05-7P
87153-06-8P 87153-07-9P 87153-08-0P
87153-09-1P 87153-10-4P 87153-11-5P
87153-12-6P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as blood platelet aggregation inhibitor)

L9 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:498806 CAPLUS
DOCUMENT NUMBER: 99:98806
TITLE: Studies on 2-oxoquinoline derivatives as blood platelet aggregation inhibitors. II. 6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline and related compounds
AUTHOR(S): Nishi, Takao; Tabusa, Fujio; Tanaka, Tatsuyoshi; Shimizu, Takefumi; Kanbe, Toshimi; Kimura, Yukio; Nakagawa, Kazuyuki
CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan
SOURCE: Chem. Pharm. Bull. (1983), 31(4), 1151-7
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 99:98806
GI



I

AB A series of .omega.-(1-substituted-5-tetrazolylalkoxy)-2-oxo-tetrahydro- or dihydro-quinolines I (R = H, Me, Et, COMe, etc; R1 = H, cyclohexyl, Et, cyclooctyl, alkylpyridine, etc.) were synthesized and tested for inhibitory activity towards collagen- and ADP-induced aggregation of rabbit blood platelets in vitro. These compds. were prepd. by the reaction of 1-substituted-5-(.omega.-chloroalkyl)-tetrazoles and hydroxy-2-oxoquinolines in the presence of a base. Among them,

6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline (I; R = H, R1 = cyclohexyl) [73963-46-9] was found to have the most potent inhibitory activity. The structure-activity relationships are discussed.

IT 73963-29-8P 73963-31-2P 73963-32-3P 73963-33-4P 73963-34-5P
73963-35-6P 73963-36-7P 73963-37-8P 73963-38-9P **73963-42-5P**
78760-12-0P 78760-13-1P 78760-14-2P 86843-22-3P 86843-23-4P
86843-24-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT 59-31-4DP, tetrazolylalkoxy derivs. 73963-46-9P 73963-48-1P
73963-50-5P 73963-51-6P 73963-55-0P 73963-56-1P 73963-59-4P
73963-60-7P 73963-61-8P **73963-62-9P** 73963-63-0P
73963-64-1P 73963-68-5P 73963-69-6P 73963-70-9P 73963-71-0P
73963-72-1P 73963-74-3P 73963-77-6P 73963-78-7P
73963-87-8P 73963-91-4P 78876-16-1P 78876-17-2P 85163-74-2P
86843-25-6P 86843-26-7P 86843-27-8P 86843-28-9P 86843-29-0P
86843-30-3P 86843-31-4P 86843-32-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and blood platelet aggregating inhibitory activity of, structure in relation to)

L9 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1980:426293 CAPLUS
DOCUMENT NUMBER: 93:26293
TITLE: Therapeutic tetrazolylalkoxycarbostyril derivatives
PATENT ASSIGNEE(S): Otsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Belg., 47 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 878548	A1	19791217	BE 1979-196976	19790831
JP 55035019	A2	19800311	JP 1978-107869	19780901
JP 61055514	B4	19861128		
CA 1139761	A1	19830118	CA 1979-334272	19790822
DE 2934747	A1	19800313	DE 1979-2934747	19790828
DE 2934747	C2	19880128		
AU 7950397	A1	19800306	AU 1979-50397	19790829
AU 538410	B2	19840816		
US 4277479	A	19810707	US 1979-70710	19790829
DK 7903631	A	19800302	DK 1979-3631	19790830
DK 158788	B	19900716		
DK 158788	C	19901210		
FI 7902699	A	19800302	FI 1979-2699	19790830
FI 68398	B	19850531		
FI 68398	C	19850910		
NL 7906523	A	19800304	NL 1979-6523	19790830
NL 183888	B	19880916		
NL 183888	C	19890216		
SU 1064868	A3	19831230	SU 1979-2804457	19790830
SE 7907236	A	19800302	SE 1979-7236	19790831
SE 432252	B	19840326		
SE 432252	C	19840705		
NO 7902829	A	19800304	NO 1979-2829	19790831
NO 153177	B	19851021		
NO 153177	C	19860129		
FR 2434809	A1	19800328	FR 1979-21869	19790831

FR 2434809	B1	19820917			
ZA 7904627	A	19800827	ZA 1979-4627	19790831	
ES 483792	A1	19800901	ES 1979-483792	19790831	
CH 641799	A	19840315	CH 1979-7920	19790831	
GB 2033893	A	19800529	GB 1979-30520	19790903	
GB 2033893	B2	19821201			
AT 7905845	A	19810315	AT 1979-5845	19790903	
AT 364363	B	19811012			

PRIORITY APPLN. INFO.: JP 1978-107869 19780901

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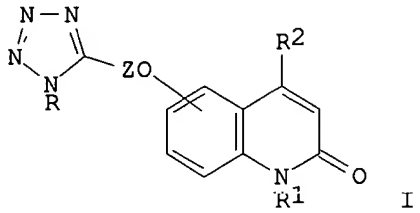

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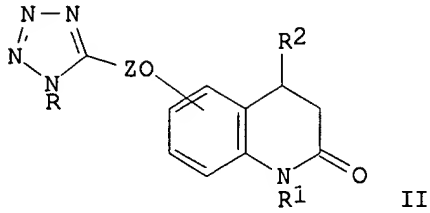

II

AB Monohydroxycarbostyrils were O-alkylated by 5-(.omega.-haloalkyl)tetrazoles to give (tetrazolylalkoxy)carboxstyrils I and II [R = alkyl, cycloalkyl, cycloalkylalkyl, Ph, phenylalkyl; Z = alkylene (the tetrazolylalkoxy group is in the 4-, 5-, 6-, 7-, or 8-position); R1 = H, alkyl, alkenyl, alkanoyl, benzoyl, phenylalkyl; or R2 = H, alkyl], which inhibited blood platelet aggregation, inhibited cyclic AMP phosphodiesterase, and showed vasodilator activity; I and II are useful as antiinflammatory and anti-ulcer agents (no data). 6-Hydroxycarbostyril reacted with 1-cyclohexyl-5-(3-chloropropyl)tetrazole and K2CO3 in DMF at 70-80.degree. to give the resp. I [R1 = R2 = H, Z = (CH2)3, R = cyclohexyl].

IT 73963-46-9P 73963-50-5P 73963-56-1P 73963-59-4P 73963-60-7P
73963-62-9P 73963-63-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and pharmacol. activity of)

IT 73963-51-6P 73963-52-7P 73963-53-8P 73963-54-9P 73963-55-0P
73963-58-3P 73963-61-8P 73963-69-6P 73963-70-9P 73963-71-0P
73963-72-1P 73963-73-2P 73963-74-3P 73963-75-4P
73963-78-7P 73963-79-8P 73963-85-6P 73963-86-7P 73963-87-8P
73963-88-9P 73963-89-0P 73963-90-3P 73963-91-4P 73974-41-1P
73974-43-3P 73974-44-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT 73963-29-8P 73963-32-3P 73963-33-4P 73963-34-5P 73963-36-7P
73963-37-8P 73963-38-9P **73963-42-5P** 73963-43-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, and O-alkylation of hydroxycarbostyrils by)

=> file casreact
FILE 'CASREACT' ENTERED AT 11:23:22 ON 16 SEP 2002

FILE CONTENT:1974 - 15 Sep 2002 VOL 137 ISS 11

Some records from 1974 to 1991 are derived from the ZIC/VINITI data file and provided by InfoChem.

This file contains CAS Registry Numbers for easy and accurate substance identification.

Crossover limits have been increased. See HELP RNCROSSOVER for details.

Structure search limits have been raised. See HELP SLIMIT for the new, higher limits.

=> d que
L1 STR

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.
L3 6 SEA FILE=CASREACT SSS FUL L1 (21 REACTIONS)

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L3 ANSWER 1 OF 6 CASREACT COPYRIGHT 2002 ACS
ACCESSION NUMBER: 136:183828 CASREACT
TITLE: Preparation of cilostazol
INVENTOR(S): Mendelovichi, Marioara; Finkelstein, Nina; Pilarksi, Gideon
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014283	A1	20020221	WO 2001-US25398	20010814

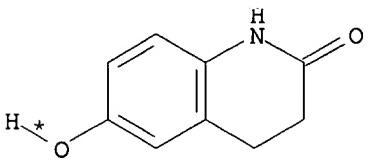
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001084887	A5	20020225	AU 2001-84887	20010814
US 2002099213	A1	20020725	US 2001-929683	20010814
PRIORITY APPLN. INFO.:			US 2000-225362P	20000814
			US 2000-190588P	20000320
			WO 2001-US25398	20010814

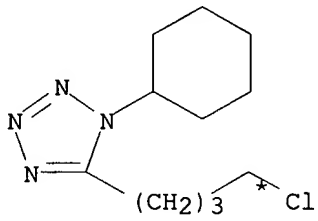
AB The present invention provides processes for prepg. cilostazol {6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone} and processes for purifying the same by recrystn. Thus, 6-hydroxy-3,4-dihydroquinolinone, KOH, K2CO3, 5-(4-chlorobutyl)-1-cyclohexyl-1H-tetrazole, and n-BuOH are heated at reflux for 5 h to give 84% cilostazol. Cilostazol inhibits cell platelet aggregation and is used to treat patients with intermittent claudication (no data).

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

RX(1) OF 2 A + **B** ===> **C**

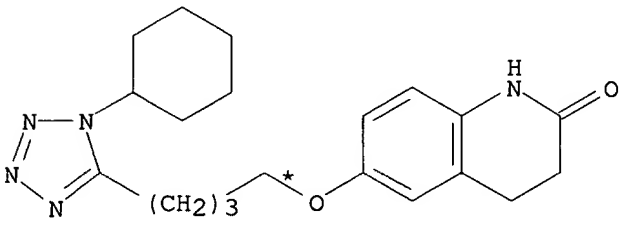


A



B

(1)

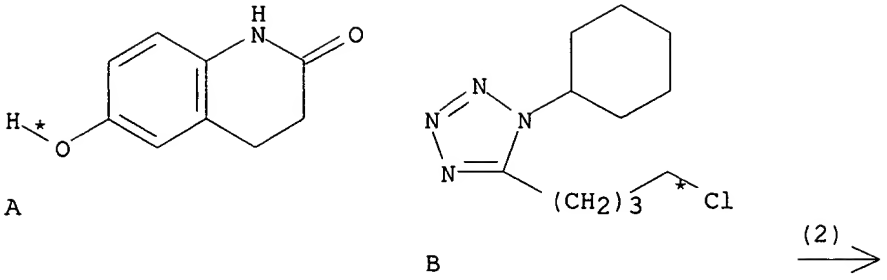


C

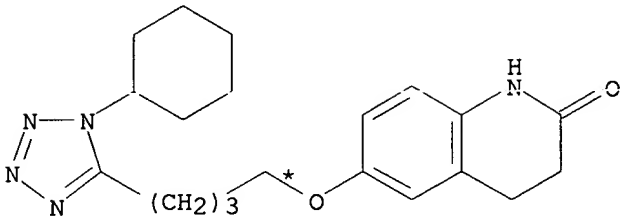
YIELD 94%

RX(1) RCT A 54197-66-9, B **73963-42-5**
RGT D 1310-58-3 KOH, E 584-08-7 K2CO3
PRO C **73963-72-1**
SOL 71-36-3 BuOH
NTE alternative prepns. gave lower yields

RX(2) OF 2 A + **B** ===> **C**



A B (2)



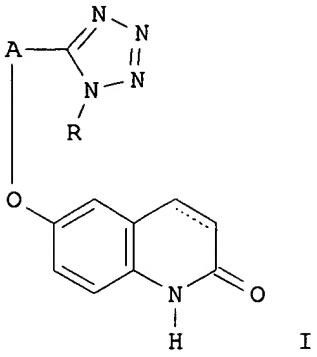
C
YIELD 88%

RX(2) RCT A 54197-66-9, B **73963-42-5**
RGT G 1310-73-2 NaOH, H 7757-82-6 Na2SO4
PRO C **73963-72-1**
CAT 10108-86-8 1-Octanaminium, N,N,N-trimethyl-, chloride
SOL 108-88-3 PhMe, 7732-18-5 Water
NTE alternative catalysts also used

L3 ANSWER 2 OF 6 CASREACT COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:137510 CASREACT
TITLE: Process for the preparation of tetrazolylalkoxycarbostyril derivatives
INVENTOR(S): Aki, Shinji; Kurimura, Muneaki; Nishi, Takao; Nankawa, Junichi; Tominaga, Michiaki; Fukuyama, Norihiro; Yamamoto, Akihiro
PATENT ASSIGNEE(S): Ohtsuka Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001213877	A2	20010807	JP 2000-339018	20001107
PRIORITY APPLN. INFO.:			JP 1999-332559	19991124

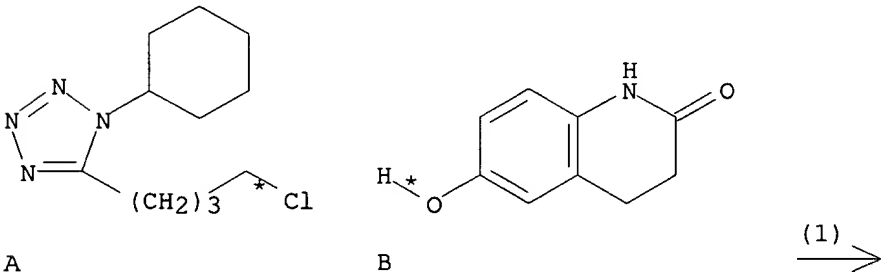
OTHER SOURCE(S): MARPAT 135:137510
GI



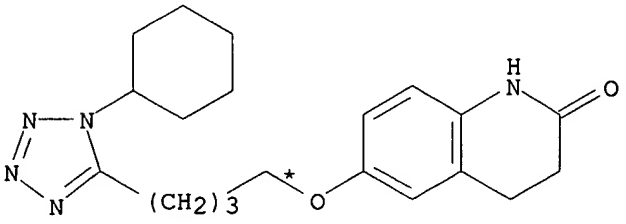
I

AB The title compds. I [A = alkylene; R = cycloalkyl; the dotted line indicates a single or double bond] are prepd., e.g. by reaction of 6-hydroxy-3,4-dihydrocarbostyril with a haloalkyltetrazole deriv. in the presence of a phase transfer catalyst (e.g., tetrabutylammonium chloride). I are useful as antithrombotics, inflammation inhibitors, antiulcer agents (no data), etc. 6-[4-(1-Cyclohexyl-1,2,3,4-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril was prepd. in 95% yield by the title process.

RX(1) OF 1 **A** + B ===> **C**



A B (1)



C
YIELD 95%

RX(1) RCT A **73963-42-5**, B 54197-66-9
RGT D 584-08-7 K2CO3, E 7757-83-7 Na2SO3
PRO C **73963-72-1**
CAT 1112-67-0 Bu4NCl
SOL 7732-18-5 Water, 108-88-3 PhMe

L3 ANSWER 3 OF 6 CASREACT COPYRIGHT 2002 ACS ✓

ACCESSION NUMBER: 103:141893 CASREACT

TITLE: Studies on 2-oxoquinoline derivatives as blood platelet aggregation inhibitors. IV. Synthesis and biological activity of the metabolites of 6-[4-(1-cyclohexyl-1H-5-tetrazolyl)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (OPC-13013)

AUTHOR(S): Nishi, Takao; Tabusa, Fujio; Tanaka, Tatsuyoshi; Shimizu, Takefumi; Nakagawa, Kazuyuki

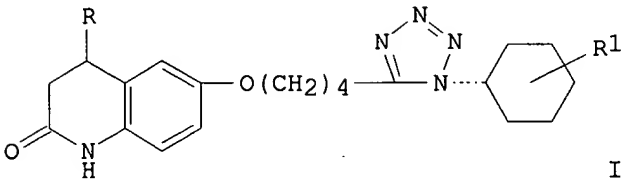
CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan

SOURCE: Chem. Pharm. Bull. (1985), 33(3), 1140-7
CODEN: CPBTAL; ISSN: 0009-2363

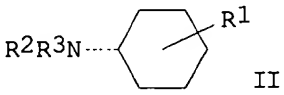
DOCUMENT TYPE: Journal

LANGUAGE: English

GI



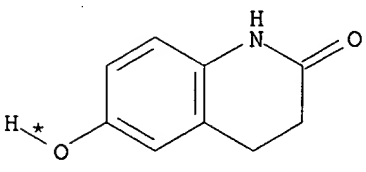
I



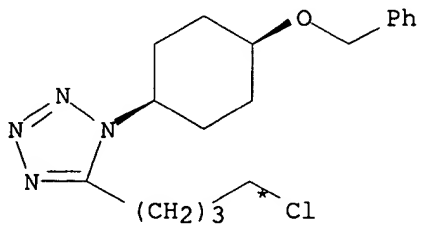
II

AB Metabolites of (I; R = R1 = H) were prepd. Thus, cyclohexanolamides II (R1 = 2.alpha.-, 2.beta.-, 3.alpha.-, 3.beta.-, 4.alpha.-, 4.beta.-OH, R2 = H, R3 = Ac) were benzylated to give 61-84% II (R1 = OCH2Ph), which were hydrolyzed to give 76-89% II (R1 = OCH2Ph, R2 = R3 = H). Acylation of the amines with Cl(CH2)4COCl gave 80-98% II [R1 = OCH2Ph, R2 = H, R3 = CO(CH2)4Cl], which typically gave .apprx.95% II [R2R3 = N:NN:C(CH2)4Cl] upon treatment with PCl5-HN3. Coupling of these compds. with 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline, followed by hydrogenolysis, gave I (R = H, R1 = OH). I (R = OH, R1 = H) was also prepd. in 5 steps from 5,2-HO(O2N)C6H3CHO. I (R = H, R1 = 3.alpha.-, 4.alpha.-, 4.beta.-OH; R = OH, R1 = H) were identified as metabolites of OPC-13013, with I (R = H, R1 = 3.alpha.-4.alpha.-OH) showing almost equiv. platelet aggregation-inhibitory activities.

RX(31) OF 147 ...AU + **AL** ===> **AV**...

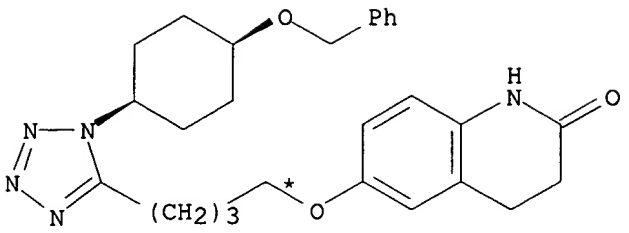


AU



AL

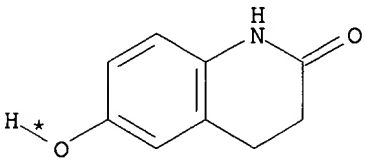
(31) ⟶



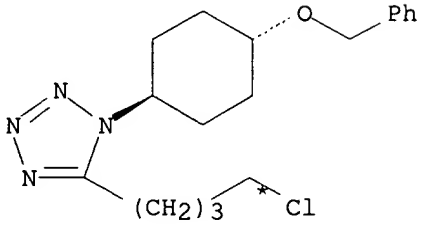
AV

RX(31) RCT AU 54197-66-9, AL **98454-49-0**
RGT U 1310-58-3 KOH
PRO AV **87152-99-6**
SOL 67-63-0 Me2CHOH

RX(32) OF 147 ...AU + **AP** ===> **AX**...

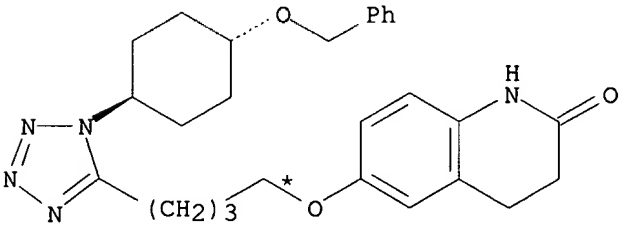


AU



AP

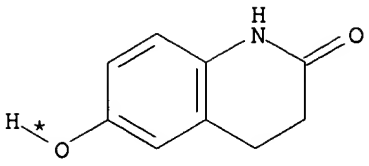
(32)



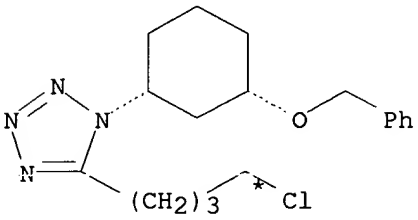
AX

RX(32) RCT AU 54197-66-9, AP **98454-50-3**
RGT U 1310-58-3 KOH
PRO AX **87152-97-4**
SOL 67-63-0 Me2CHOH

RX(33) OF 147 ...AU + **AQ** ===> **AY**...

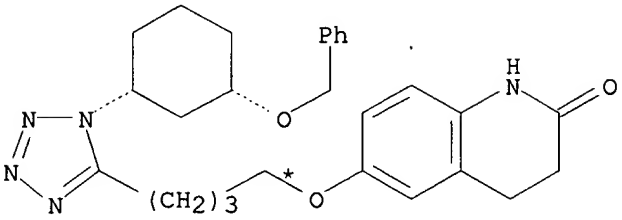


AU



AQ

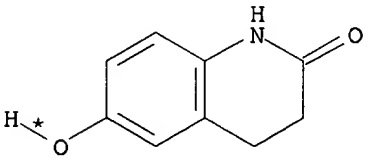
(33)



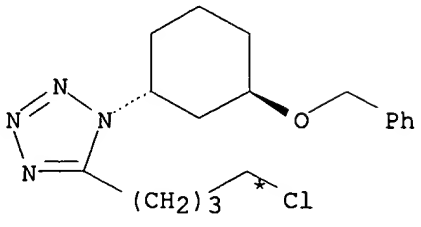
AY

RX(33) RCT AU 54197-66-9, AQ **98454-51-4**
RGT U 1310-58-3 KOH
PRO AY **98454-55-8**
SOL 67-63-0 Me2CHOH

RX(34) OF 147 ...AU + **AR** ===> **AZ**...

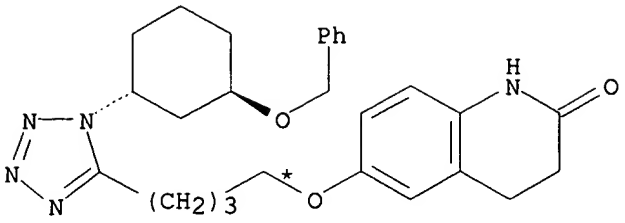


AU



AR

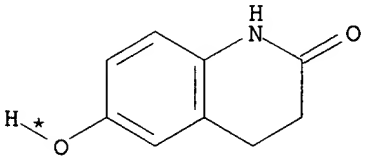
(34)



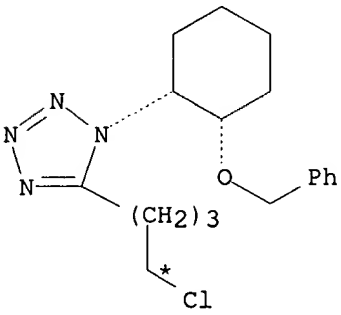
AZ

RX(34) RCT AU 54197-66-9, AR **98454-52-5**
RGT U 1310-58-3 KOH
PRO AZ **87153-00-2**
SOL 67-63-0 Me2CHOH

RX(35) OF 147 ...AU + **AS** ===> **BA**...

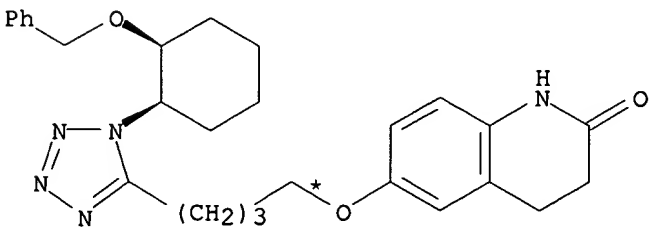


AU



AS

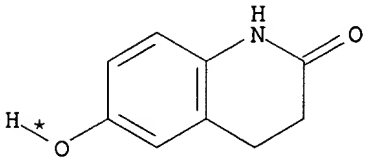
(35)



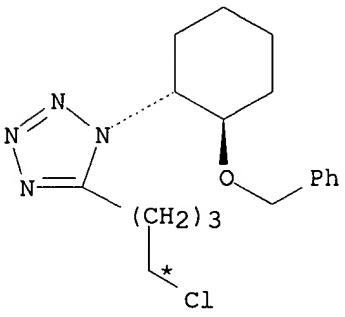
BA

RX(35) RCT AU 54197-66-9, AS **98454-53-6**
RGT U 1310-58-3 KOH
PRO BA **87152-98-5**
SOL 67-63-0 Me2CHOH

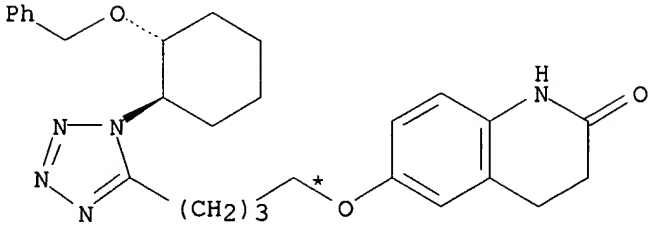
RX(36) OF 147 ...AU + **AT** ===> **BB**...



AU



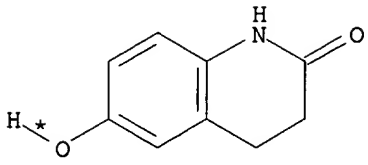
AT (36) ⟶



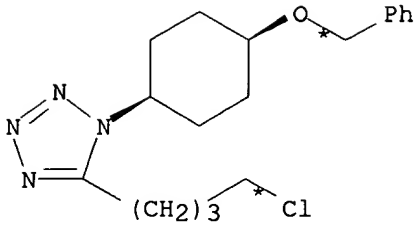
BB

RX(36) RCT AU 54197-66-9, AT **87153-14-8**
RGT U 1310-58-3 KOH
PRO BB **87153-12-6**
SOL 67-63-0 Me2CHOH

RX(72) OF 147 COMPOSED OF RX(31), RX(37)
RX(72) AU + **AL** ===> **BC**

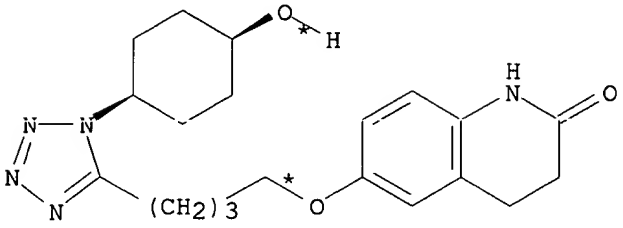


AU



AL

2 STEPS

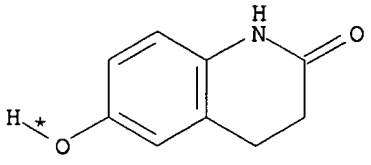


BC

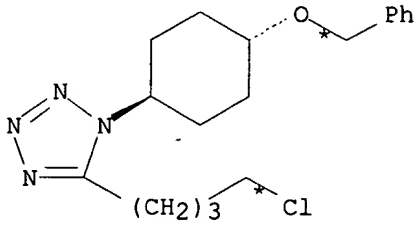
RX(31) RCT AU 54197-66-9, AL **98454-49-0**
RGT U 1310-58-3 KOH
PRO AV 87152-99-6
SOL 67-63-0 Me2CHOH

RX(37) RCT AV 87152-99-6
RGT BD 1333-74-0 H2
PRO BC **87153-06-8**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

RX(73) OF 147 COMPOSED OF RX(32), RX(38)
RX(73) AU + **AP** ===> **BH**

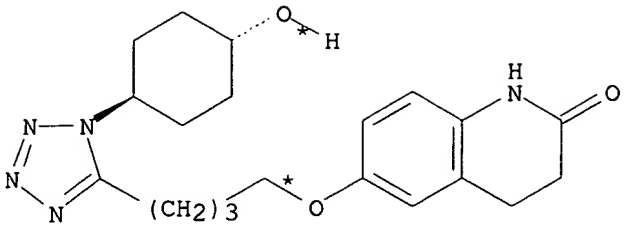


AU



AP

2 STEPS

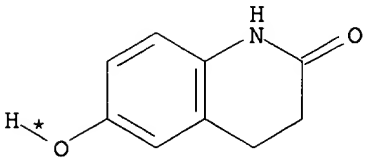


BH

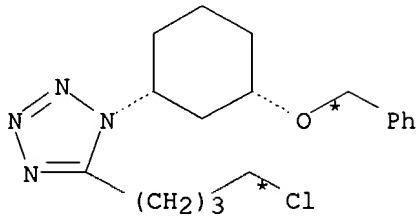
RX(32) RCT AU 54197-66-9, AP **98454-50-3**
RGT U 1310-58-3 KOH
PRO AX 87152-97-4
SOL 67-63-0 Me2CHOH

RX(38) RCT AX 87152-97-4
RGT BD 1333-74-0 H2
PRO BH **87153-04-6**
CAT 7440-05-3 Pd
SOL 64-19-7 AcOH, 67-56-1 MeOH

RX(74) OF 147 COMPOSED OF RX(33), RX(39)
RX(74) AU + **AQ** ===> **BI**

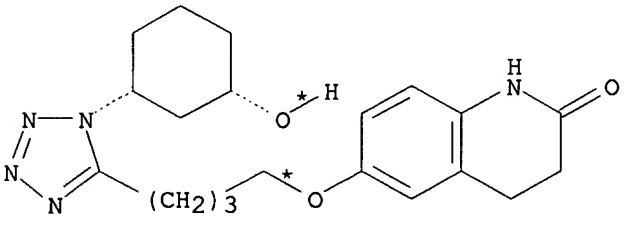


AU



AQ

2 STEPS



BI

RX(33) RCT AU 54197-66-9, AQ **98454-51-4**
RGT U 1310-58-3 KOH
PRO AY 98454-55-8
SOL 67-63-0 Me2CHOH